Agricultural Pesticide Use, Familial Cancer, and Risk of Non-Hodgkin Lymphoma

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Abstract

To investigate whether the association between agricultural pesticide use and the risk of non-Hodgkin's lymphoma (NHL) is modified by a family history of hematopoietic cancer, including leukemia, myeloma, and lymphoma, we analyzed pooled data on white men from three population-based, case-control studies of NHL conducted in Iowa/Minnesota, Kansas, and Nebraska. Information on the agricultural use of insecticides, fungicides, and herbicides; a family history of cancer; and other risk factors was obtained by interviewing 973 cases and 2,853 controls or, if deceased, their next-of-kin (37% of cases, 43% of controls). The NHL risk was estimated by odds ratios (ORs) and 95% confidence intervals (CIs), adjusted for age, state of residence, type of respondent, and use of hair dye. Compared to men with no family history of cancer, the ORs (95% CIs) of NHL was 1.5 (1.3–1.8) for men with a family history of nonhematopoietic cancer, and 2.7 (1.9–3.7) for those with a history of hematopoietic cancer among first-degree relatives. This positive association was noted for each group of NHL defined according to the Working Formulation, and was most pronounced for small lymphocytic NHL. Among direct respondents, farmers who used pesticides and had a positive family history of cancer or hematopoietic cancer were not at elevated risk of NHL, compared to nonfarmers who had no family cancer history. However, among proxy respondents, ORs were elevated for farmers who had a positive family history of hematopoietic cancer and used animal insecticides (OR = 4.6; 1.9–11.2), crop insecticides (OR = 4.7; 1.6–13.4), or herbicides (OR = 4.9; 1.7–14.2), although the interaction of family history of cancer and agricultural pesticide use was not statistically significant. In summary, the joint effects of the family cancer history and pesticide use were limited to proxy respondents with wide CIs and, thus, provide little evidence that a family history of cancer modifies the association of agricultural exposures with NHL. (Cancer Epidemiol Biomarkers Prev 2004;13(4):525–531)

Introduction

Non-Hodgkin's lymphoma (NHL) is a cancer of the immune system. Except for primary immunodeficiency disorders (1) or acquired immune alterations (2), there are few well-established risk factors for NHL. A family history of NHL or hematopoietic cancer, including leukemia, multiple myeloma, and lymphoma in close relatives has been consistently associated with a 2- to 3-fold higher risk of NHL (3–6). In addition, agricultural pesticide use has been linked with NHL in several studies (7–13), but not all (14–16). Because individuals from families with recurrent hematopoietic cancer might inherit genetic features that increase their susceptibility to NHL, the impact of environmental or other potential cancer-causing agents on the risk of NHL may differ among individuals with and without a family history of hematopoietic cancer. An evaluation of the separate and combined effects of family cancer history and agricultural pesticide use may provide insights regarding NHL etiology.

To date, few epidemiological studies have assessed the association of NHL with agricultural exposures by family history of cancer (3, 10, 17). Zhu *et al.* (17) found that chlorinated hydrocarbon pesticides were associated with a higher risk of NHL among subjects with a family history of hematopoietic cancer, but not among those without a family history. Linet and Pottern (3) observed a significant excess of NHL in subjects who had both a family history of hematopoietic cancer and occupational exposure to gasoline or benzene, when compared to nonexposed individuals without a positive family history. The risk was lower, although still significantly elevated, among individuals with a positive family history but no work exposure to these substances. Zahm *et al.* (10) reported that pesticide-related risks for NHL were greater among women with a family history of cancer, particularly a history of hematopoietic cancer among first-degree relatives. These findings suggest a role for genetic susceptibility in the association of agricultural exposures with NHL.

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To further address the independent and joint contributions of family history and agricultural pesticide use to the risk of NHL, we analyzed pooled data from three population-based, case-control studies conducted in four Midwestern states, which included 973 cases and 2853 controls.

Materials and Methods

Study Population. Data from three population-based, case-control studies of NHL conducted in Iowa/Minnesota (18), Kansas (9), and Nebraska (10, 11) during the 1980s were pooled for this analysis. We evaluated NHL among white men because few women in the Nebraska study (the only investigation to include women) reported agricultural use of pesticides.

In the Iowa/Minnesota study, all newly diagnosed cases of NHL among white men, age 30 years or older, were identified from records of the State Health Registry of Iowa and a special surveillance of Minnesota hospital and pathology laboratory records (n = 780). The diagnostic period for eligibility was between March 1981 and October 1983 in Iowa, and between October 1980 and September 1982 in Minnesota. In Minnesota, cases who resided in the cities of Minneapolis, St. Paul, Duluth, or Rochester at the time of diagnosis were excluded because the original study focused on agricultural exposures. In Kansas, all cases of NHL among white men, age 21 years or older, diagnosed between 1979 and 1981, were identified through the University of Kansas Cancer Data Service, a statewide tumor registry. A sample of 200 men was randomly selected from the 297 NHL cases diagnosed during the eligible time period. In the Nebraska study, all cases of NHL diagnosed between July 1983 and June 1986 among white subjects age 21 years or older and living in one of the 66 counties of eastern Nebraska were identified through the Nebraska Lymphoma Study Group and area hospitals (n = 227). In the three studies, study pathologists reviewed the tumor slides for all patients and classified the NHL according to the Working Formulation (19). The pathology reviews were done in each study before pooling the data. Only histologically confirmed cases were included in this analysis.

Controls without hematopoietic cancer were randomly selected from the same geographical area as the cases with frequency matching by age (5-year age groups), sex, race, state of residence, and vital status at the time of interview using a 2:1 matching ratio in Iowa and Minnesota, and approximately 4:1 in Kansas and Nebraska. Controls for living cases under 65 years of age were randomly selected by two-stage, random digit dialing, as described by Waksberg (20). For living cases 65 years or older, the controls were a simple random sample from the records of the Health Care Financing Administration (Medicare). Controls for deceased cases were selected from death records in each state and matched to the cases by age, sex, race, and year of death. A total of 3379 controls (Iowa and Minnesota, 1543; Kansas, 1005; and Nebraska, 831) were identified.

In Iowa/Minnesota, 694 of 780 presumptive NHL cases were interviewed (89%). After pathology review of the interviewed cases, 622 were confirmed as NHL. Interviews also were obtained from 1245 controls (81%) in Iowa/Minnesota. In Kansas, 170 cases and 948 controls were interviewed, yielding interview response rates of 96% and 94%, respectively. In Nebraska, 201 cases and 725 controls were interviewed, yielding interview response rates of 91% and 87%, respectively. After accounting for the household census response rate, the overall response rates for controls were 78% in Iowa and Minnesota, 90% in Kansas, and 85% in Nebraska. Combining the three studies, interviews were obtained from 993 eligible male cases and 2918 male controls. Individuals lacking information regarding living or working on a farm were excluded from this report. In addition, subjects who did not provide information on date of birth or a family history of cancer were excluded from the pooled data set, leaving a total of 973 cases and 2853 controls eligible for the pooled analysis.

Data Collection. Interviews were conducted directly with the subjects, or with their next-of-kin if the subjects were deceased or incapacitated. The interviews were conducted by telephone in Kansas and Nebraska, and in person in Iowa and Minnesota. In Iowa, Minnesota, and Nebraska, subjects were asked whether they had used or personally handled specific pesticides; whether the pesticides were used on crops, animals, or both; the year of first use and last use; and the year of use for specific pesticides. In Kansas, however, duration and intensity measures were obtained for insecticides as a group and herbicides as a group, but not for individual pesticides. The specific chemicals used were reported in an open-ended question at the end of each section. Thus, for the Kansas data, the years and frequency of use refer to the broad categories, not specific chemicals.

Participants were also asked to provide a family history of cancer among blood relatives, including the types of cancer. Each of the three studies also collected detailed information on demographic characteristics and tobacco use. However, not all studies collected the same information on hair dye use, alcohol use, occupational exposures, and medical conditions.

Data Analysis. Subjects who had never lived or worked on a farm as an adult were defined as nonfarmers, and were used as the reference population. Our analyses for the associations of family history of cancer used only data on the parents, brothers, sisters, and children (first-degree relatives) because of the low reliability of data on second-degree relatives (21). The presence of hematopoietic cancer in at least one first-degree relative was considered a positive family history of hematopoietic cancer. A family history of cancer was defined as having cancers other than hematopoietic cancer among first-degree relatives. We used hematopoietic cancer rather than NHL as the definition of a positive family history because: (*a*) hematopoietic stem cells are the common cell of origin for a variety of hematological cancers including NHL; (*b*) both hematological cancers and NHL may share common risk factors; and (*c*) respondents may not be able to distinguish between the various types of hematopoietic cancer when they report a family history of NHL or other hematological cancers.

The maximum likelihood estimate of the odds ratio (OR) (22) and the 95% confidence interval (CI) were used

as the measure of association between exposure categories and risk of NHL. Analyses were also conducted for four histological groups according to the Working Formulation (19): follicular NHL (Working Formulation categories B–D), diffuse large cell NHL (Working Formulation categories G and H), small lymphocytic NHL (Working Formulation category A), and other NHL (Working Formulation categories E, F, I, J, and miscellaneous). Multiple logistic regression analysis was used to adjust for the potential confounding effects of age (20–44, 45–64, 65–74, ≥75 years), state of residence (Iowa/Minnesota, Kansas, and Nebraska), type of respondent (direct or proxy interview), and use of hair dye (yes, no, missing). Selection of potential confounders was based on biological importance, statistical significance, and the availability of data for all three study sites, except hair dye use where a category was created to include missing data from the Kansas study. Due to high collinearity among pesticide groups, we did not mutually adjust for these exposures in our analyses. Information on HIV infection was not available. However, it seems unlikely that HIV infection was a significant confounder or risk factor for NHL in the present study, given the time period (*i.e.*, early to mid-1980s), location (*i.e.*, four Midwestern states where HIV infection and AIDS were not common), and age of the participants (*i.e.*, 86% of the cases and 81% of the controls were older than 50 years of age).

To evaluate possible effect modification of the pesticide-NHL association by a family history of cancer, cases and controls were classified by both family cancer history and agricultural pesticide use, and ORs were calculated for a positive family history, with or without pesticide use, and for a negative family history with pesticide use, each category being compared with the absence of both. Interaction was tested by a likelihood ratio test comparing the model with interaction terms and a model containing only the main effects. Analyses were conducted using SAS (SAS Institute, Cary, NC) software programs. The reported *P* values are two-sided.

Results

Characteristics of study subjects and possible risk factors for NHL are shown in Table 1. There were 973 cases and 2853 controls in the combined study. The number of subjects by state of residence was 607 cases and 1213 controls for Iowa and Minnesota; 166 cases and 927 controls for Kansas; and 200 cases and 713 controls for Nebraska. The proportion of proxy interviews was comparable between case and control groups within each study site. The age distributions of cases and controls were similar, except in Kansas where a higher proportion of controls in the youngest group was noted. Cases and controls were also similar with respect to education, marital status, and tobacco use. However, in comparison with the controls, cases were more likely to have used hair dye (Iowa/Minnesota), lived or worked on a farm (Kansas), and more likely to have first-degree relatives with cancer or hematopoietic cancer (all three studies).

Table 2 shows multivariable-adjusted ORs for NHL associated with a family history of cancer and agricultural pesticide use according to respondent status. There was about a 1.5-fold risk of NHL for men with a family history of any cancer other than hematopoietic cancer and almost a 3-fold risk of NHL for those with a history

Table 1. Characteristics of NHL case and control subjects[a]

	Iowa and Minnesota				Kansas				Nebraska			
	Cases		Controls		Cases		Controls		Cases		Controls	
	n	(%)	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)
Total subjects	607		1213		166		927		200		713	
Respondent status												
Self	425	(70.0)	812	(66.9)	78	(47.0)	450	(48.5)	111	(55.5)	355	(49.8)
Proxy	182	(30.0)	401	(33.1)	88	(53.0)	477	(51.5)	89	(44.5)	358	(50.2)
Age (yrs)												
20–44	56	(9.2)	86	(7.1)	18	(10.8)	229	(24.7)	17	(8.5)	68	(9.5)
45–64	204	(33.6)	373	(30.8)	50	(30.1)	230	(24.8)	56	(28.0)	193	(27.1)
65–74	157	(25.9)	347	(28.6)	47	(28.3)	205	(22.1)	59	(29.5)	194	(27.2)
≥75	190	(31.3)	407	(33.6)	51	(30.7)	263	(28.3)	68	(34.0)	258	(36.2)
Smoking												
No	114	(18.8)	282	(23.3)	50	(30.1)	216	(23.3)	73	(36.5)	182	(25.5)
Yes	492	(81.2)	931	(76.8)	116	(69.9)	710	(76.7)	127	(63.5)	531	(74.5)
Used hair dye												
Never	558	(91.9)	1157	(95.3)	NA[b]		NA		186	(93.0)	657	(92.2)
Ever	47	(7.7)	49	(4.0)					14	(7.0)	55	(7.7)
Family history of cancer												
No	274	(45.1)	649	(53.5)	59	(35.5)	532	(57.4)	104	(52.0)	460	(64.5)
Nonhematopoietic cancer	285	(47.0)	513	(42.3)	104	(62.6)	391	(42.2)	68	(34.0)	211	(29.6)
Hematopoietic cancer	48	(7.9)	51	(4.2)	3	(1.8)	4	(0.4)	28	(14.0)	42	(5.9)
Farming												
Nonfarmer	150	(24.7)	305	(25.1)	37	(22.3)	279	(30.1)	54	(27.0)	181	(25.4)
Farmer	457	(75.3)	908	(74.9)	129	(77.7)	648	(69.9)	146	(73.0)	532	(74.6)

[a]The percentages do not always sum to 100 because of missing data.
[b]NA = not applicable.

Table 2. Risk of NHL associated with family cancer history and agricultural exposure to pesticides among male farmers according to respondent status

	Direct interviews				Proxy interviews				All subjects	
	Cases	Controls	OR[a]	(95% CI)[b]	Cases	Controls	OR	(95% CI)	OR	(95% CI)
Family cancer history										
No	283	976	1.0	referent	154	665	1.0	referent	1.0	referent
Nonhematopoietic cancer	279	583	1.6	(1.3–1.9)	178	532	1.5	(1.1–1.9)	1.5	(1.3–1.8)
Hematopoietic cancer	52	58	2.7	(1.8–4.0)	27	39	2.6	(1.5–4.5)	2.7	(1.9–3.7)
Agricultural exposures										
Nonfarmers	164	437	1.0	referent	77	328	1.0	referent	1.0	referent
Animal insecticides										
Farmers (no use)	101	355	0.9	(0.7–1.3)	88	361	1.3	(0.9–1.9)	1.1	(0.8–1.4)
Farmers (used)	273	650	1.0	(0.8–1.3)	123	357	1.3	(0.9–1.8)	1.1	(0.9–1.3)
Crop insecticides										
Farmers (no use)	187	576	0.9	(0.7–1.2)	112	453	1.2	(0.8–1.6)	1.0	(0.8–1.2)
Farmers (used)	178	410	1.1	(0.8–1.4)	84	215	1.6	(1.1–2.3)	1.2	(1.0–1.5)
Fungicides										
Farmers (no use)	307	859	0.9	(0.7–1.2)	172	618	1.2	(0.9–1.7)	1.0	(0.8–1.2)
Farmers (used)	57	135	1.0	(0.9–1.9)	20	68	1.5	(0.8–2.6)	1.3	(1.0–1.8)
Herbicides										
Farmers (no use)	170	513	0.8	(0.7–1.2)	103	435	1.1	(0.8–1.6)	1.0	(0.8–1.2)
Farmers (used)	201	482	1.0	(0.8–1.3)	93	248	1.6	(1.1–2.3)	1.2	(1.0–1.5)

[a]OR = odds ratios adjusted for age (20–44, 45–64, 65–74, ≥75 years), state of residence (Iowa/Minnesota, Kansas, Nebraska), type of respondent (direct or proxy interview, all subjects only), and use of hair dye (yes, no, missing).
[b]CI = confidence interval.

of hematopoietic cancer among first-degree relatives. The ORs were similar irrespective of respondent types. In contrast, for agricultural pesticide use, the ORs obtained using proxy data were, in general, larger than using direct data. Among direct respondents, farmers reporting using pesticide groupings of insecticides, fungicides, or herbicides showed no higher risk of NHL than nonfarmers, whereas the ORs for NHL from proxy interviews were elevated among farmers who used insecticides on crops or herbicides.

A family history of cancer among first-degree relatives increased the risk of NHL, regardless of the specific histological types (Table 3). The risk appeared to be somewhat stronger for small lymphocytic NHL (OR = 3.6) than follicular NHL (OR = 2.8), diffuse large cell NHL (OR = 2.8), and other NHLs (OR = 2.6). Agricultural pesticide use was weakly associated with the risk of developing small lymphocytic NHL and other NHL, but not follicular NHL or diffuse large cell NHL. Farmers were at nearly 3-fold higher risk of developing small lymphocytic NHL if they had used fungicides (OR = 2.8; 1.4–5.6). The risks of developing other NHL were approximately 40% higher among farmers who used herbicides or insecticides on crops.

Table 3. Risk of NHL for family cancer history and agricultural exposure to pesticides by histologic type[a] in Iowa/Minnesota, Kansas, and Eastern Nebraska

	Controls	Follicular NHL		Diffuse large cell NHL		Small lymphocytic NHL		Other NHL	
		Cases	OR (95% CI)[b]	Cases	OR (95% CI)	Cases	OR (95% CI)	Cases	OR (95% CI)
Family cancer history									
No	1641	129	1.0 (referent)	119	1.0 (referent)	41	1.0 (referent)	139	1.0 (referent)
Nonhematopoietic cancer	1115	127	1.6 (1.2–2.1)	130	1.6 (1.2–2.1)	59	2.0 (1.3–3.0)	138	1.4 (1.1–1.8)
Hematopoietic cancer	97	23	2.8 (1.7–4.6)	23	2.8 (1.7–4.6)	11	3.6 (1.8–7.4)	22	2.6 (1.5–4.2)
Agricultural exposures									
Nonfarmers	765	76	1.0 (referent)	75	1.0 (referent)	21	1.0 (referent)	66	1.0 (referent)
Animal insecticides									
Farmers (no use)	716	41	0.9 (0.6–1.4)	62	1.0 (0.7–1.4)	21	1.3 (0.7–2.6)	63	1.2 (0.8–1.8)
Farmers (used)	1007	115	1.0 (0.7–1.4)	98	0.9 (0.6–1.2)	54	1.4 (0.8–2.3)	124	1.3 (0.9–1.8)
Crop insecticides									
Farmers (no use)	1029	76	0.9 (0.6–1.3)	87	0.8 (0.6–1.1)	35	1.1 (0.6–1.9)	100	1.2 (0.9–1.7)
Farmers (used)	625	73	1.0 (0.7–1.5)	68	1.0 (0.7–1.4)	36	1.6 (0.9–2.9)	79	1.4 (1.0–1.9)
Fungicides									
Farmers (no use)	1477	129	0.9 (0.7–1.3)	133	0.8 (0.6–1.2)	56	1.2 (0.7–2.0)	156	1.2 (0.9–1.7)
Farmers (used)	203	17	0.9 (0.5–1.6)	17	0.9 (0.5–1.6)	16	2.8 (1.4–5.6)	24	1.4 (0.9–2.4)
Herbicides									
Farmers (no use)	948	70	0.9 (0.6–1.3)	73	0.7 (0.5–1.0)	38	1.3 (0.7–2.3)	90	1.2 (0.8–1.6)
Farmers (used)	730	84	1.0 (0.7–1.5)	78	1.0 (0.7–1.4)	35	1.4 (0.8–2.5)	92	1.4 (1.0–2.0)

[a]Histology: Follicular (Working Formulation B–D), diffuse (Working Formulation G–I), small lymphocytic (Working Formulation A), other (Working formulation E, F, J, and miscellaneous).

We evaluated the joint effects of a family history of cancer and agricultural pesticide use where the reference group was subjects without a family history of cancer who had never farmed (Table 4). Among direct respondents, there was no evidence of synergism between agricultural use of insecticides, fungicides, or herbicides and a family history of cancer. The joint effects were stronger among proxy respondents, especially farmers with hematopoietic cancer among first-degree relatives who also reported the use of insecticides on animals (OR = 4.6; 1.9–11.2) or crops (OR = 4.7; 1.6–13.4), or ever used herbicides (OR = 4.9; 1.7–14.2), when compared with nonfarmers who had no family history of cancer. However, none of the *P* values for interaction were statistically significant (data not shown). Similarly, the joint effects were stronger for small lymphocytic NHL, especially from proxy respondents, compared to follicular NHL and diffuse large cell NHL (data not shown), but the point estimates lack precision due to very wide CIs.

Discussion

This pooled analysis of data from three population-based, case-control studies confirms that a family history of cancer, particularly hematopoietic cancer among first-degree relatives, is associated with a higher risk of NHL, regardless of histological type. Our findings are consistent with previous studies (3–5), including reports from some of these data (6). Risks of NHL among farmers who did not use pesticides are similar to the risk for nonfarmers, but farmers who used insecticides on crops, fungicides, or herbicides, had a slight excess risk of NHL, primarily among proxy respondents. Follicular and diffuse large cell NHL were not associated with any category of pesticide use. Small lymphocytic NHL tended to be associated with several of the pesticides groups, especially fungicides. Small excesses were also observed for the category of ''other NHL.'' ORs from joint effects of family history of cancer and agricultural pesticide use tended to be larger than ORs from these factors separately, but the ORs in the joint effect cells for direct respondents were not much different than those among nonfarmers with a family history of cancer. Somewhat larger ORs were observed in the joint effect cell among proxy respondents; it is unclear why proxies should show a stronger relationship than direct interviews. Overall, these data provide little evidence that the risks of NHL associated with the use of insecticides, fungicides, and herbicides differs according to family history of cancer.

It is plausible that NHL might aggregate in families because of inherited defects in immune function or other genetic changes that place carriers at increased risk for the disease (23). Familial aggregation may also relate to a shared environmental exposure among the family members. For example, a case study reported NHL in three genetically unrelated family members living in the same household (24). Another study reported an increased risk of hematopoietic cancer, including NHL, among marital couples (25), and people with prior social contact (26). However, the extent to which familial susceptibility and the effects of environmental agents contribute to lymphomagenesis remains largely unknown.

The few epidemiological studies that assessed the association of agricultural exposures and NHL risk according to a family cancer history among first-degree relatives (3, 17) or among first- and second-degree relatives (10) suggest that individuals with a positive family history may have an increased susceptibility to the effects of agricultural exposures. This hypothesis is consistent with the findings by Alavanja *et al.* (27) in which several specific pesticides were associated with higher risk of prostate cancer among study subjects with a family history of prostate cancer but not among those with no family history. In the present study, we also found that, among proxy respondents, the risks of NHL associated with use of insecticides and herbicides were greater among farmers with a family history of

Table 4. Risk of NHL by family history and agricultural exposure to pesticides among male farmers according to respondent type in Iowa/Minnesota, Kansas, and Eastern Nebraska

	Direct respondents			Proxy respondents		
	No family history	Nonhematopoietic cancer	Hematopoietic cancer	No family history	Nonhematopoietic cancer	Hematopoietic cancer
	OR (95% CI)[a]	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Nonfarmers	1.0 (referent)	1.4 (0.9–2.1)	2.5 (1.1–5.8)	1.0 (referent)	1.5 (0.9–2.5)	2.0 (0.6–6.7)
Animal insecticides						
Farmers (no use)	0.9 (0.6–1.4)	1.4 (0.9–2.1)	1.8 (0.6–5.0)	1.2 (0.7–2.0)	2.1 (1.2–3.4)	2.9 (0.8–10.3)
Farmers (used)	1.0 (0.7–1.3)	1.4 (1.0–2.0)	2.3 (1.3–4.4)	1.4 (0.9–2.3)	1.6 (1.0–2.5)	4.6 (1.9–11.2)
Crop insecticides						
Farmers (no use)	0.9 (0.6–1.2)	1.3 (0.9–1.9)	2.4 (1.2–4.8)	1.1 (0.7–1.9)	1.6 (1.0–2.6)	3.1 (1.2–7.9)
Farmers (used)	1.1 (0.8–1.5)	1.5 (1.0–2.1)	1.7 (0.8–3.9)	1.6 (0.9–2.7)	2.1 (1.3–3.6)	4.7 (1.6–13.4)
Fungicides						
Farmers (no use)	0.9 (0.6–1.2)	1.3 (1.0–1.8)	2.1 (1.2–3.8)	1.3 (0.8–2.0)	1.6 (1.0–2.5)	3.5 (1.5–8.4)
Farmers (used)	1.4 (0.8–2.4)	1.5 (0.9–2.6)	2.7 (0.7–11.6)	1.0 (0.4–2.6)	2.7 (1.2–5.8)	3.3 (0.5–21.5)
Herbicides						
Farmers (no use)	0.9 (0.6–1.3)	1.3 (0.9–1.9)	1.8 (0.9–3.7)	1.1 (0.7–1.9)	1.4 (0.9–2.3)	3.2 (1.3–7.8)
Farmers (used)	1.0 (0.7–1.4)	1.5 (1.0–2.1)	2.7 (1.3–5.9)	1.5 (0.9–2.6)	2.2 (1.3–3.6)	4.9 (1.7–14.2)

[a]OR adjusted for age (20–44, 45–64, 65–74, ≥75 years), state of residence (Iowa/Minnesota, Kansas, Nebraska), and use of hair dye (yes, no, missing).

hematopoietic cancer, compared to farmers without a family history. However, this difference was not statistically significant, and this may be due to small sample size.

Evidence from several studies suggests that risks for some risk factors may apply to only certain NHL subtypes (6, 28–30). It is possible that individuals with a positive family history may have an increased susceptibility to the effects of agricultural exposures, but perhaps only for certain subtypes of NHL or for specific pesticides or chemical classes. In the present study, the associations were slightly stronger for small lymphocytic NHL and ''other'' NHL, as compared to follicular NHL, diffuse large cell NHL, or NHL as a whole group. Moreover, pesticides have diverse chemical and different biological modes of action, and only a few appear to be carcinogenic in bioassays. Thus, grouping pesticides by type (as done in this pooled analysis) may group quite dissimilar chemicals. Consequently, analysis by specific pesticides within the general chemical classes may be more important etiologically (31–34). However, the number of cases with a positive family history and exposure to specific pesticides in most studies, including this one, is too small for precise evaluation of effect modification by family history.

Several lines of evidence suggest that pesticides may be causally related to chromosomal abnormalities or genetic mutations in NHL. Pesticide applicators who are exposed to the fumigant phosphine or who have mixed exposures to other pesticides and phosphine have been found to have a significant increase in chromosomal rearrangements in peripheral blood lymphocytes as compared to control subjects (35). Figgs *et al.* (36) also reported that the urinary concentration of 2,4-dichlorophenoxyacetic acid, a herbicide that has been associated with NHL, was linked to increased peripheral blood lymphocyte replicative index scores among herbicide applicators. A recent use of data from the Iowa/Minnesota case-control study by Schroeder *et al.* (37) found that the risk of NHL associated with dieldrin, toxaphene, lindane, atrazine, and fungicides was limited to only cases with the t(14;18) chromosomal translocation, which occurs commonly in follicular lymphoma and a subset of diffuse large B-cell lymphoma (38, 39). They found that a family history of hematopoietic cancer was associated with t(14;18)-negative NHL, but not t(14;18)-positive NHL (40).

Our study has several strengths. The pooled studies provide a relatively large number of subjects with detailed information on pesticide use. The studies included in the pooled analysis had high response rates (89–96% for cases and 77–93% for controls), included only newly diagnosed, histologically confirmed cases of NHL that occurred in defined time periods, randomly selected control subjects representative of the population at large, and collected information on many potential confounding factors.

One limitation of the present study is that self-report of family history was not validated with medical records so they may not be a good surrogate for genetic susceptibility. Self-reporting of cancer in first-degree relatives has been shown to be relatively accurate (41). In a case-control study of 437 NHL cases in Yorkshire, England, the OR was only slightly reduced when the analysis was restricted to confirmed (by medical record) occurrences of leukemia or lymphoma among relatives (42). Evaluation of possible recall bias among chronic lymphocytic leukemia cases, cancer controls, and non-cancer controls in a case-control study showed little evidence of differential recall regarding a family history among cancer *versus* non-cancer subjects (43).

Another potential limitation is that cases may differentially report their agricultural pesticide use compared with controls, which may bias the risk estimates. Blair and Zahm (31) evaluated the patterns of pesticide use among farmers classified on an ever/never basis in the Kansas study, one of the study sites in this pooled analysis, and concluded that a differential misclassification is unlikely in this data set. However, our finding of greater ORs among proxy respondents than direct respondents is a concern because proxies cannot provide information on pesticide use as accurately as farmers themselves (44, 45). Proxy respondents have also been found to be more likely to give ''don't know'' answers (46). It remains possible, however, that the larger ORs among proxies than direct interviews are due to larger risk among deceased farmers who may have had a more aggressive disease (*i.e.*, diffuse large cell NHL). Finally, although we have controlled for the potential effects of geographic differences in the pooled analysis, residual confounding by study sites is possible.

In summary, the present study confirms that a family history of cancer, particularly hematopoietic cancer among first-degree relatives, is associated with an increased risk of NHL, regardless of specific NHL type. Risks of NHL for farmers who did not use pesticides are similar to those of nonfarmers, but farmers who used insecticides on crops, fungicides, or herbicides had a slight excess risk of NHL, which was more apparent among proxy respondents. Analysis of the joint effects of the family cancer history and agricultural pesticide use suggests that the risk of NHL associated with insecticides and herbicides was slightly greater among farmers with a family history of cancer or hematopoietic cancer among first-degree relatives, especially from proxy respondents. However, none of the interactions was statistically significant, and small sample size precludes definite interpretation. Overall, these data provide little evidence that individuals with a positive family history may have an increased susceptibility to the effects of agricultural exposures.

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